REMARKS/ARGUMENTS

Status

Claims 1-20 are under examination. Claims 31-39 are added in this amendment.

Applicants acknowledge with appreciation the Examiner's withdrawal of prior rejections under 102(b) and 102(e) and prior rejection under 37 CFR 1.75.

Claim 1 remains rejected as allegedly anticipated by Mandecki *et al.*

Claims 1-20 are rejected as allegedly obvious over Lebedenko *et al.* in view of both Gokhale *et al.* and Slater *et al.*

The undersigned applicants' representative contacted Examiner Popa on November 7 to request a telephonic interview to discuss the rejections of record. Examiner Popa agreed to such an interview. Applicants appreciate the Examiner's consideration.

Organization of response

The claims discussed in four groups, each of which will be addressed in turn.

First, independent claims 1, and dependent claims 31-34

Second, independent claim 2, and dependent claims 3-13.

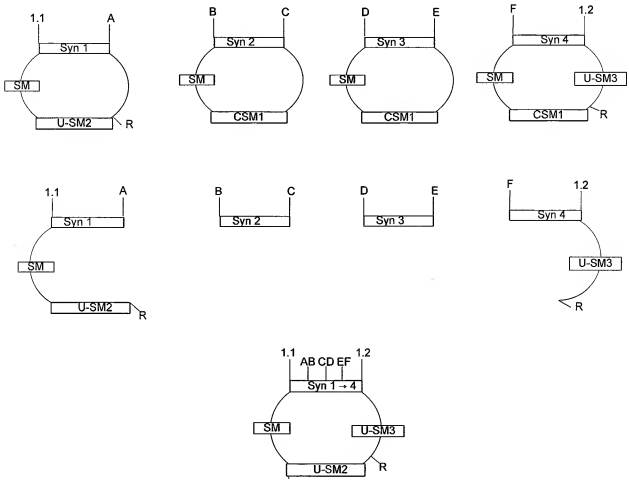
Third, independent claim 14, and dependent claims 15-20.

Fourth independent claim 35, and dependent claims 36-39.

The Invention

The inventors have provided a novel method that allows rapid, economic and efficient preparation of artificial genes. Unlike the prior art methods described by the Office, the invention provides a practical method for making very large synthetic genes (e.g., including genes greater than 20 kbp in length) by a process including simultaneous ligation of multiple fragments. The claimed method makes use of a combination of three different types of vectors (see Figures 20A, B, C and D), and, in contrast to prior art methods, does not require multiple rounds of purification of short isolated inserts (e.g., by gel electrophoresis). Eliminating the need for isolation and recloning of small polynucleotide fragments is a significant advantage not found in the references relied on by the Office.

The diagram below is based on Figure 20 of the application and provides a schematic illustration of the invention.[1] The illustration shows four vectors containing adjacent sequences or segments of the synthetic gene (top row), digestion products containing the segments (middle row) and the product of simultaneous ligation of the digestion products to form a new vector comprising the four joined sequences. Keeping in mind that many other digestion products and ligation products will be formed in addition to those shown in the middle row, the method allows selection of the desired product based on a pair of selectable markers (U-SM2 and U-SM3) present in only the desired product. The method also allows elimination of undesired product based on counterselectable markers. The resulting vector (bottom row) may be used in additional rounds of digestion, ligation and selection.



[1] It will be appreciated, and Applicants emphasize, that this description and the drawing above are illustrated and are provided to assist the Examiner in understanding the invention, but are not intended to be limiting. One of skill

The rejections of specific groups of claims will now be addressed:

Claims 1 and 31-33

Claim 1 was rejected as allegedly anticipated by Mandecki *et al.*

As previously discussed by applicants, Mandecki describes a method in which individual segments are cloned into vectors. The inserts are excised by restriction digestion, and each isolated insert is gel-purified (see, e.g., page 103, col. 2, first partial paragraph). The gel-purified fragments are then ligated to each other. The resulting ligation product is itself gel-purified. The purified ligation product is then ligated to a similarly prepared second ligation product. The full length (444-bp) fragment is then restriction digested, gel purified, and cloned into a vector. The necessity for isolation of fragments (e.g., by gel purification) is cumbersome, slow and expensive and not practical for synthesis of large synthetic genes. Indeed, the production of a 444-bp fragment required three different gel purification steps and numerous separate ligation steps.

Mandecki did not describe or suggest the method now claimed. Although the Office asserts that Mandecki teaches that a ligation product is selected based on a selectable marker, Applicants respectfully submit this is not correct. While Mandecki describes identifying *transformants* into which inserts are cloned using lacZ, Mandecki did not describe selecting a *ligation product* based on a selectable marker. According to Mandecki's method, ligation products are selected using *gel electrophoresis* (i.e., by size), the very process that can be advantageously avoided using the present method.

The Office also asserts that the Mandecki reference teaches using "at least three different DNA vectors" as recited in claim 1. Although Mandecki described different vectors, they are not used together in a coordinated fashion, or even in the same synthesis, as are the three vector types of the instant invention. Rather, Mandecki's vectors are used only to clone segments in one of three different reading frames vis-à-vis a lac Z gene, or for segments containing a stop codon. The Mandecki method may be carried out using a single vector rather than involving coordinated use of multiple vectors .

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reading the specification and claims would understand that numerous variations of the method described in the specification and/or will be apparent to one of skill who has read the disclosure.

Moreover, the claims that depend from claim 1 further distinguish the invention from the Mandecki reference. Claims 31-32 specify that the selectable marker is a drug resistance gene, not found in Mandecki. Claim 34 specifies that the ligation product is selected based on two different selectable markers, each from different vector, which was not described or suggested by Mandecki *I.*

Therefore, Applicants respectfully request this rejection be withdrawn.

Claims 2-13

Claims 2-13 were rejected as allegedly obvious in view of the combination of Lebedenko *et al.*, Gokhale *et al.* and Slater *et al.*

The Office's argument is that Lebedenko *et al.* described a method for synthesis of a gene and Slater et al. described the use of selectable markers. [2] Initially Applicants note that almost the whole of claim 2 has not been taken into account by the Office. The Office makes the sweeping assertion that the use of selectable markers and/or counterselectable markers (apparently in any combination, in any process, and for any result) is "not innovative" because the art teaches diverse selectable and counter-selectable markers and "one of skill would know how to select markers to ensure that all inserts are present in the final product." Applicants respectfully disagree. The use of restriction sites and selectable markers to build synthetic genes as claimed and described in the specification is highly innovative and allows, *inter alia*, rapid and economical gene synthesis without the intervening isolation of fragments and required by methods such as the Lebedenko method (see Lebedenko pages 6760 col. 2, first full paragraph and page 6758, col. 1, second full paragraph *for example*).

[2] Gokhale *et al.* is cited only to show motivation to make PKS genes. Applicants respectfully disagree with the Office's characterization of the reference as well as with the Office's characterization of Applicant's comments in the response filed October 17, 2006 (e.g., Applicants did not argue that Gokhale *et al.* was nonanalogous art as indicated in the Office Action). In any event, Gokhale is relevant, if at all , only to claims 11 and 12 which call out polyketide synthase genes . Gokhale et al. does not remedy the deficiencies of the primary references (discussed below) with regard to claims 11 and 12, or any other claim. For clarity the reference is not further addressed in this analysis. Applicants do no waive any right to distinguish Gokhale reference in future prosecution.

Moreover, the Office has entirely ignored the elements of any dependent claims (other than citation of Gokhale et al. in connection with claims 11 and 12[3]).

Applicants reiterate that broad unsupported statements asserting obviousness do not make a *prima facie* case. Thus, the statement "one of skill in the art *would know to use the right combination* of selectable and counter-selectable markers for the selection of the desired product" is unsupported and incorrect. Using the Lebedenko method, ligation products were selected by PAGE (see p. 6760) not using selectable markers. The Office fails to suggest any reason the Lebedenko would be modified to add selectable and counter-selectable markers to the DNA fragments to be ligated or vectors carrying them, and does not provide any basis or indication one of skill would know *how* to accomplish what the Applicants have invented. The claimed methods were not known and are not suggested by the references relied on by the Office.

Further, as noted in Applicant's previous response, the Office has not explained how or why the method of Lebedenko would have been modified to use three DNA vectors.[4] In addressing this the Office states that Lebedenko described three different pUC19 plasmids and incorrectly asserts that "the specification discloses that the Type 1, 2 and 3 molecules differ only with respect to the selectable markers" (Office Action page 7, citing paragraph 0230 of the published application, US 2005/0227316). This is not correct. Paragraph 0230 does not contain the word "only." Claim 2 itself plainly recites specific differing characteristics of the Type 1, Type 2 and Type 3 molecules. Finally, reference to paragraphs [0231[-[0235[, the Figures, and the remainder of the specification illustrates that Type I, Type 2 and Type 3 vectors have other differences, not limited to the position of the selectable marker with relation to other vector elements.

Similarly, the broad assertion that "one of skill *would know* to use more than one molecule, depending on the gene needed to be synthesized" in addition to being wholly

[3] For example, the Office does not discuss how an element in Claim 3 ("selecting transformants that express said first and second selectable markers and do not express said first, second, or third counter-selectable marker") is suggest by the cited references.

[4] Although the Office asserted, "It is noted that this limitation was not present in the original set of claims and it was introduced by the amendment to the claims filed on 02/08/2007 . . " Applicants disagree. See original claim 2, which recited a Type 1 DNA molecule, a Type 2 DNA molecule and at least one Type 3 DNA molecule, each with different characteristics. The specification, e.g., Figure 20, is replete in teaching that a fundamental aspect of the invention is the coordinated use of structurally distinct vectors.

unsupported, would not, even if true, suggest the present invention, in which vectors with specific characteristics are used in a coordinated fashion to make a synthetic gene. Applicants respectfully submit that an assertion by the Office that "one of skill would know" does not provide any legally cognizable basis for an obviousness rejection and, in fact, is essentially impossible for Applicants to respond to it.

To support a rejection based on obviousness, the Office must address all claim limitations, and must explain with specificity why one of ordinary skill in the art would have been motivated to carry out the claimed method. The references cited by the Office neither described nor suggested Applicant's method invention and the Office has provided no reason one of skill would have modified elements in the references to arrive at the claimed invention.. Applicants respectfully request this rejection be withdrawn.

Claims 14-20

Claims 14-20 are directed to compositions comprising particular DNA molecules. The Office has not provided any basis for the rejection of claims 14-20 and therefore has not established *prima facie* obviousness. Applicants respectfully submit these claims are allowable and the rejection should be withdrawn.

Claims 35-39

Independent claims 35 and dependent claims 36-39 are new and have not been previously examined. These claims are directed to the method disclosed in the specification and Figures, such as the process illustrated at page 10 of this paper.

Related application

Applicants note that related, commonly owned application No. 10/672396 (published August 26, 2004 as US 2004/0166567 and cited as reference 3 in the information disclosure statement filed April 3, 2006) is copending and also relates to methods for making synthetic genes. Claims to synthetic gene compositions are under examination in that application.

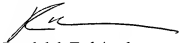
Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-462-5330.

Date: November 14, 2007

Respectfully submitted,



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